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the haplotype structure. No further circularization of the long-range PCR products is required, nor would such circularization be of any benefit for this method.

In contrast, Applicants have disclosed and claimed "A method for determining the haplotype structure of a contiguous DNA segment comprising a first nucleotide polymorphism (NP) and a second NP separated by at least 200 nucleotides" using the following steps: First, "obtaining a DNA sample comprising said contiguous DNA segment;" second "using said DNA sample as a template for polymerase chain reaction (PCR) amplification of a DNA fragment comprising said contiguous DNA segment;" third, "ligating the ends of said DNA fragment to each other so as to produce a circular DNA molecule;" and fourth, "determining the haplotype...." Applicants' method utilizes PCR to produce the template for the subsequent steps.

To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP § 2143.

The present rejection fails on the first point because no evidence has been provided to support a motivation to combine Patel with the method of Michalatos-Beloin. The requirement for the establishment of motivation to combine references is central to the obviousness inquiry, and has been explained by the Federal Circuit in the following manner:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See*, *e.g.*, *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).

"The factual inquiry whether to combine references must be thorough and searching." *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See*, *e.g.*, *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding") (quoting C.R. Bard, Inc., v. M3 Systems,

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Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("teachings of references can be combined only if there is some suggestion or incentive to do so.") (emphasis in original) (quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In re Lee, 277 F.3d 1338, 61 U.S.P.Q.2d 1430, 1433-4 (Fed. Cir. 2002)(vacating and remanding the decision of the Board for failing to follow the relevant precedent).

In the present rejection, the objective evidence of record does not support a conclusion that one of skill in the art would have been motivated to combine Patel and Michalatos-Beloin.

As an initial matter, the office action states that "[a]n ordinary practitioner would have been motivated to use long range PCR as the template for the DARMSI-PCR method of Patel rather than genomic DNA in order to permit improved discrimination and detection as taught by Michalatos-Beloin (see page 4867, column 2)..." (emphasis added). Clarification is requested regarding this statement: Examiner's representative has diligently reviewed this reference and has been unable to find support for such teaching.

If the office action is referring to the statement in column 2 of page 4867 that "[s]ingle base pair differences may not have the robustness of an insertion/deletion polymorphism...[,]" Applicants request consideration of the entire quote: "Single base pair differences may not have the robustness of an insertion/deletion polymorphism but separate analysis using each of the two allele-specific primers will serve as mutual confirmations as illustrated at the CD4 locus in Figure 4." See the last sentence of the first full paragraph, page 4867, column 2. According to this statement, the method taught by Michalatos-Beloin could detect all haplotypes, even single base pair differences, without further manipulations. Therefore, this statement confirms the absence, rather than the presence, of any motivation or reason to modify the method taught by Michalatos-Beloin.

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The office action also asserts that "Michalatos-Beloin teaches haplotyping methods where the molecules are prepared by long-range PCR...." From this, it is concluded that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the long range PCR method of Michalatos-Beloin to prepare the sample for the haplotyping method of Patel since Michalatos-Beloin states 'The allele-specific long range PCR products were used as templates for amplification of the STR..." Applicants disagree with this characterization of the Michalatos-Beloin method. Michalatos-Beloin did not use the PCR step to prepare a sample for additional manipulations such as ligation, etc. Rather, in the Michalatos-Beloin method, haplotyping is conducted by PCR. One need only analyze the PCR products of the Michalatos-Beloin method to determine the haplotype of the source DNA. Michalatos-Beloin did confirm the accuracy of their long-range PCR method by amplifying the short-tandem repeat from the long-range PCR product, but this step was carried out to prove that the long-range PCR method accurately determined haplotype without further manipulations or additional steps.

The office action also finds motivation to combine in the following quote from Michalatos-Beloin: "The ability to isolate hemizygous DNA segments readily from heterozygous genomes via molecular haplotyping will provide the accuracy necessary in these diverse applications' (page 4867, column 2)." However, the quoted language would not provide the motivation to combine Michalatos-Beloin with Patel. Indeed, it would not motivate any modification of Michalatos-Beloin at all. Instead, the statement touts the utility of the Michalatos-Beloin method and teaches away from its modification or combination with any other method.

Significantly, the office action does not refer to Patel for any motivation to combine the references. Patel teaches that the circularization/linearization step (which brings the polymorphism sites closer together than they are naturally found in the genome) prior to inverse ARMS PCR is necessary because "PCR cannot be done when the primers are separated by longer than a few kilobases." Patel, page 3565, column 1. Were it not for the difficulties of carrying out haplotyping by PCR over long distances, the circularization step Patel resorted to

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would not be necessary. Thus, Patel teaches away from its combination with Michalatos-Beloin because Michalatos-Beloin teaches the feasibility of haplotyping by PCR over long distances. In other words, Michalatos-Beloin solves the problem identified by Patel that necessitated the circularization step in the first place. The art worker would be motivated to utilize Michalatos-Beloin *instead* of Patel, not to combine the two.

For all these reasons, no motivation to select the components of Applicants' method has been established and no findings beyond those discussed above have been made in support of the present rejection. It should therefore be withdrawn. *See In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)(specific findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components of the claimed invention); *In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984)(mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification).

Moreover, there is no evidence in the office action that the combination of Patel and Michalatos-Beloin would yield a method operable for its intended purpose. For instance, the method of Michalatos-Beloin is intended to provide allele discrimination by long-range PCR using allele specific PCR primers that are not designed for circularization. Therefore, the system of Michalatos-Beloin is not compatible with the additional manipulations of Patel. *Tec Air Inc.* v. Denso Manufacturing Michigan Inc., 52 U.S.P.Q.2d 1294, 1298 (Fed. Cir. 1999)(a combination of references that would produce a device inoperable for its intended purpose teaches away from combining same).

Based upon this analysis of the prior art, it is clear that the teaching, motivation, or suggestion to select and combine the references has not been demonstrated. In fact, because the references teach away from their combination, the Examiner has not carried his burden in supporting his obviousness determination.

To summarize, nothing in the record demonstrates that one of skill in the art would have had the motivation to combine Patel and Michalatos-Beloin. Indeed, the present rejection

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constitutes a hindsight-based obviousness determination. For all of these reasons, Applicants respectfully request that the rejection be withdrawn.

Claim 17 is rejected under 35 U.S.C. § 103 over Patel and Michalatos-Beloin in further view of Krynetski *et al.* (1995) *Proc. Natl. Acad. Sci.*, 92:949-953. Applicants respectfully traverse.

As described above, there is no motivation to combine Patel and Michalatos-Beloin. Krynetski merely teaches a point mutation of the TPMT gene and thus does not satisfy the deficiencies of the primary references. Consequently, the motivation to combine these three references has not been established and the rejection should be withdrawn.

Claim 18 is rejected under 35 U.S.C. § 103 over Patel and Michalatos-Beloin in further view of Martin et al. (2000) Am. J. Hum. Genet., 67:383-394. Applicants respectfully traverse.

As already explained, there is no motivation to combine Patel and Michalatos-Beloin. Martin teaches SNPs in the region surrounding the APOE gene but does not satisfy the deficiencies of the primary references. Accordingly, the motivation to combine these three references has not been established and the rejection should be withdrawn.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicant respectfully submits that the rejections of the claims under 35 U.S. C. § 103 are overcome. Applicant submits that this application is now in condition for allowance. Early notice to this effect is solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed October 12, 2001, has not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed

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copy of the Form 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Form 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted.

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Box Non-Fee Amendment, Commissioner for Patents, Washington, DC 20231, on November 8, 2002.